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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/044,671	01/10/2002	Katrina L. Mealey	4630-61733	9719

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EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/044,671	MEALEY ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-13,22 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *several* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I in the paper received by the office on 10/14/2003 is acknowledged. Applicant's arguments filed 10/14/03 have been fully considered but are not considered to be persuasive to rejoin Examiner's groups I and V in the restriction requirement sent 9/9/2003. In view of claim cancellations, claims 1, 2, 4-13, 22 and 27 are now pending and claims 1, 2, and 4-13 will be examined herein. Applicant's election with traverse of Group I is acknowledged. The traversal is on the ground(s) that the inventions of Groups I and V are not independent and distinct, and that there is no serious burden on the examiner to examine the claims together. The examiner maintains that each group is characterized by a patentably distinct invention and would require different searches that would create a burden on the examiner. The applicants also traverse on the grounds that the office did not provide a process of using the nucleic acid of Group V that is materially different from the processes encompassed in Group I. An alternative process could be the use of the products in Group V as probes that comprise a microarray for various expression detection assays. Furthermore, applicant should note that in addition to the inventions being patentably distinct and causing a search burden, the two groups are classified in different Classes and subclasses(see restriction requirement) and even further, art can be applied that anticipates the claims of Group V that could not do the same for those claims of Group I.

The applicant is reminded:

> The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include

all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

The examiner maintains the restriction requirement made previously, as each group is correctly separated as unrelated or patentably distinct and as such makes the restriction requirement Final.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The present application's claim to benefit of a U.S. provisional Application 60/261,578 filed 1/12/2001, is granted as is the claim to benefit of U.S. provisional Application 60/314,829 filed 8/24/2001.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1, 2, and 4-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting ivermectin sensitivity in a canine subject, comprising determining whether a gene-truncation mutation in a mdr1-encoding sequence of the subject is present in the subject, wherein the gene truncation mutation is a deletion of four base pairs at about residue 294-297 of SEQ ID NO:1, wherein the presence of the gene-truncation mutation indicates that the subject is sensitive to ivermectin, but does not reasonably provide enablement for the same method of detecting ivermectin sensitivity in any subject other than a canine subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the

predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1, 2, and 4-13 are broadly drawn to a method of detecting ivermectin sensitivity in any subject, comprising determining whether a gene-truncation mutation in a mdr1-encoding sequence of the subject is present in the subject, wherein the gene truncation mutation is a deletion of four base pairs at about residue 294-297 of SEQ ID NO:1, wherein the presence of the gene-truncation mutation indicates that the subject is sensitive to ivermectin. In fact the specification recites that the present invention provides the methods of detecting in any subject(for instance a mammal)(Pg.3 line 22). However, as will be further discussed, there is no support in the specification and prior art for the practicing of the above method of detecting in any subject, or in any mammal for that matter. The invention is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The specification recites that "the exact four-nucleotide deletion (AGAT) was detected in all (7/7) samples from ivermectin-sensitive Collies"(Pg. 10 lines 28-29). The specification also asserts in the same paragraph that "these dogs were homozygous for the deletion". The specification further asserts that "samples from all non-Collie dogs (1Beagle, 2 Golden Retrievers, and 1Staffordshire terrier cross-bred dog) were homozygous wild-type"(Pg. 10) while samples from all (6/6) ivermectin non-sensitive Collies displayed a heterozygous genotype, whit one strand carrying the mutant allele, and the other strand carrying the wild-type allele"(Pg. 10 lines 29-33). However, there is

no evidence that this same method was also used successfully on any other subject besides that of canines.

Both the prior and post-date art shows that there is a great deal of unpredictability in the practice of this method in an entirely different species and in any subject for that matter even any mammal. The prior art teaches that "ivermectin has been administered to over seven million ethnically diverse human patients at doses (mg/kg) greater than those required to induce neurotoxicity in affected collies and CF-1 mice, without evidence of the adverse effects(Brown et al. Journals of Tropical Medicine and Parasitology, 1998 92(1):S61-S64). The post filing date art further confirms the unpredictability of this area. Mealey et al. (Pharmacogenetics 2001, 11:727-733) teach that "although polymorphisms in P-gp expression and function have been documented in people, none has been associated with ivermectin sensitivity"(Pg. 732 left). The reference further states that ""it seems unlikely, therefore, that a P-gp polymorphism of this type exists in people"(732 left).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is no teaching of such a deletion mutation even being present in any other subjects, not to mention the association with ivermectin sensitivity. The fact that such mutation are not even known to exist in people for instance, makes such a claims impossible, while such a proposition in other mammals is almost prophetic without evidence to the contrary. Significant testing would have to be done of all animals for the mutation in addition to the testing of each animals' concurrent sensitivity to ivermectin. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Working Examples

The specification has no working examples of a method of detecting ivermectin sensitivity in any subject other than a canine, comprising determining whether a gene-truncation mutation in a mdr1-encoding sequence of the subject is present in the subject, wherein the gene truncation mutation is a deletion of four base pairs at about residue 294-297 of SEQ ID NO:1, wherein the presence of the gene-truncation mutation indicates that the subject is sensitive to ivermectin.

Guidance in the Specification.

The specification provides no evidence that the disclosed method is applicable to any subject. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses the methods application in a canine subject and merely prophesizes that it could be extended to any subject. There is no support for the detection of a similar 4 bp deletion mutation in any other subject types.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where there is no specific teaching of similar 4 bp deletion mutations causing ivermectin sensitivity, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art, post date filing art and the specification provide insufficient guidance to overcome the art recognized problems in the practice of such a method in any subject other than in canines. Thus given the broad claims in an art whose nature is identified as

unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

35 U.S.C. 112, Written Description Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

A review of the language of the full content of the specification indicates that *mdr1* is essential to the operation and function of the claimed invention. The specification discloses SEQ ID NO: 1 which corresponds to the nucleotide sequence of the canine *mdr1* cDNA and the P-gp amino acid sequence encoded thereby. A review of the language of the claim indicates that the claim 11 is drawn to a genus, i.e., any nucleic acid that minimally contains "an *mdr1* sequence". The claim is drawn to a nucleic acid comprising any sequence found in the *mdr1* gene. As such, the claimed method reads on obtaining from a subject any genomic sequence, any full-length gene, any splice variants or cDNAs that all contain any *mdr1* sequence. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO: 1, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an

> adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.
>
> The named ORF is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for isolating and characterizing cDNA sequences from *E. grandis*, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe *E. grandis* cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the specification does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute *E. grandis* cDNA appears in the application. Accordingly, the specification does not provide a written description of the invention of claims 1, 4, and 6-15.

Therefore, none of the sequences encompassed by the claim meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number until 1/13/2004 is (703) 306-0284 and 1/14/2004 and after will be (571)272-0748. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Jeffrey Fredman, can be reached at (703)308-6568. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)308-1119. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris

1/8/2004

JEFFREY FREDMAN
PRIMARY EXAMINER